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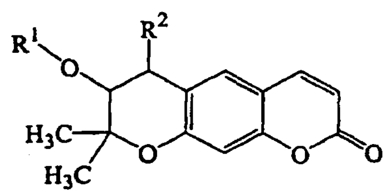
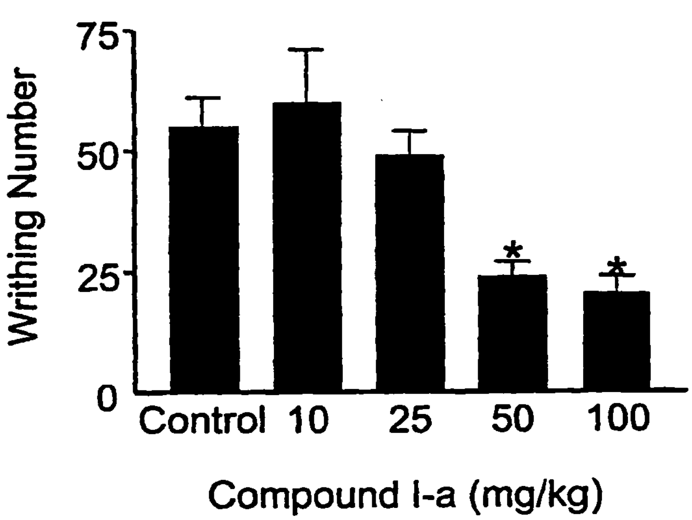
(54) Title: DECURSINOL OR DERIVATIVE THEREOF AS ANALGESIC AGENT



(I)

(57) Abstract: Decursinol and derivatives thereof represented by formula (I) can be used for alleviating pain in a mammal In said formula, R^1 is hydrogen, 3-methyl-but-2-enoyl or 2-methyl-but-2-enoyl; and R^2 is hydrogen or hydroxy.



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DECURSINOL OR DERIVATIVE THEREOF AS ANALGESIC AGENT

Field of the Invention

The present invention relates to a use of dercursinol and derivatives thereof as an analgesic agent.

Background of the Invention

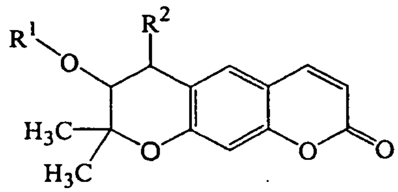
Conventional analgesics, e.g., acetaminophen and aspirin, are generally administered in a high dosage ranging from 1 g to 4 g per day, which practice often entails undesired side effects such as gastrointestinal disturbance, allergy and hepatotoxicity. Accordingly, there has existed a need to develop an analgesic which is effective at a low dosage and does not induce adverse side effects.

The pharmacological activities of decursinol, decursin and decursinol angelate isolatable from *Angelica gigas*(Chi H-J et al., *Kor. J. Pharmacology, 1*, 25-32 (1970)) are largely unknown except for the reported anti-cancer activity of decursinol angelate(Korean Patent Publication No. 187881). However, the present inventors have discovered that decursinol and certain derivatives thereof are remarkably effective analgesics.

Summary of the Invention

Accordingly, it is a primary object of the present invention to provide a novel use of decursinol and its derivatives for alleviating pain without causing adverse side effects.

In accordance with one aspect of the present invention, there is provided a use of decursinol or a derivative thereof represented by formula I for alleviating pain in a mammal:



(I)

wherein R^1 is hydrogen, 3-methyl-but-2-enoyl or 2-methyl-but-2-enoyl; and R^2 is hydrogen or hydroxy.

BRIEF DESCRIPTION OF THE DRAWINGS

The above objects and features of the present invention will become apparent from the following description of preferred embodiments taken in conjunction with the accompanying drawings, in which:

Fig. 1 shows the writhing-inhibiting activity of 7-hydroxy-8,8-dimethyl-7,8-dihydro-6*H*-pyrano[3,2-*g*]chromen-2-one(Compound I-a);

Figs. 2A and 2B represent the analgesic activities of Compound I-a at phases 1 and 2, respectively, determined for mice administered with formalin;

Fig. 3 depicts the analgesic activity of Compound I-a determined for mice administered with Substance P;

Fig. 4 demonstrates the analgesic activity of Compound I-a determined for mice administered with glutamate;

Fig. 5A presents the time-dependent analgesic activity of Compound I-a determined for mice administered with 100 mg/kg of Compound I-a after stimulating thermal nociceptor; and Fig. 5B, the dosage-dependent analgesic activity of Compound I-a determined for mice after stimulating thermal nociceptor;

Fig. 6 describes the writhing-inhibiting activity of 3-methyl-but-2-enoic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2*H*,8*H*-pyrano[3,2-*g*]chromen-3-yl ester (Compound I-b);

Figs. 7A and 7B provide the analgesic activities of Compound I-b at phases 1 and 2, respectively, determined for mice administered with formalin;

Fig. 8 offers the analgesic activity of Compound I-b determined for mice administered with Substance P;

Fig. 9 illustrates the analgesic activity of Compound I-b determined for mice administered with glutamate;

Fig. 10A exhibits the time-dependent analgesic activity of Compound I-b determined for mice administered with 100 mg/kg of Compound I-b after stimulating thermal nociceptor; and Fig. 10B, the dosage-dependent analgesic activity of Compound I-b determined for mice after stimulating thermal nociceptor;

Fig. 11 reproduces the writhing-inhibiting activity of 6,7-dihydroxy-8,8-dimethyl-7,8-dihydro-6*H*-pyrano[3,2-*g*]chromen-2-one(Compound I-c);

Figs. 12A and 2B display the analgesic activities of Compound I-c at phases 1 and 2, respectively, determined for mice administered with formalin;

Fig. 13 discloses the analgesic activity of Compound I-c determined for mice administered with glutamate;

Fig. 14 exemplifies the writhing-inhibiting activity of acetaminophen;

Figs. 15A and 15B evidence the analgesic activities of acetaminophen at phases 1 and 2, respectively, determined for mice administered with formalin;

Fig. 16 signifies the analgesic activity of acetaminophen determined for mice administered with Substance P;

Fig. 17 explicates the analgesic activity of acetaminophen determined for mice administered with glutamate;

Figs. 18A and 18B explain the time-dependent analgesic activities determined for mice administered with acetaminophen in doses of 300 and 600 mg/kg, respectively, after stimulating thermal nociceptor;

Fig. 19 indicates the writhing-inhibiting activity of aspirin;

Figs. 20A and 20B record the analgesic activities of aspirin at phases 1 and 2, respectively, determined for mice administered with formalin;

Fig. 21 yields the analgesic activity of aspirin determined for mice administered with Substance P;

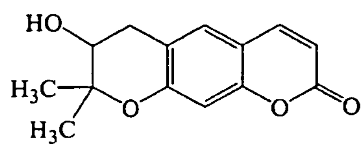
Fig. 22 gives the analgesic activity of aspirin determined for mice administered with glutamate; and

Fig. 23A compares the time-dependent analgesic activity of aspirin determined for mice administered with 100 mg/kg of aspirin after stimulating thermal nociceptor; and Fig. 23B, the dosage-dependent analgesic activity determined for mice after stimulating thermal nociceptor.

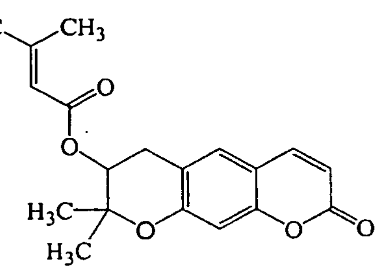
Detailed Description of the Invention

Among the compounds of formula (I), preferred are 7-hydroxy-8,8-

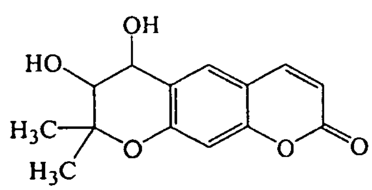
dimethyl-7,8-dihydro-6*H*-pyrano[3,2-*g*]chromen-2-one(formula I-a) which is known as decursinol; 3-methyl-but-2-enoic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2*H*,8*H*-pyrano[3,2-*g*]chromen-3-yl ester(formula I-b) which is known as decursin; 6,7-dihydroxy-8,8-dimethyl-7,8-dihydro-6*H*-pyrano[3,2-*g*]chromen-2-one(formula I-c) which is known as decursidinol; and 2-methyl-but-2-enoic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2*H*,8*H*-pyrano[3,2-*g*]chromen-3-yl ester(formula I-d) which is known as decursinol angelate.



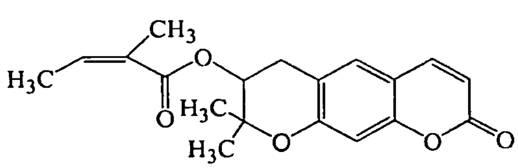
(I-a)



(I-b)



(I-c)



(I-d)

The compound of formula (I) may be used in the form of a pharmaceutically acceptable salt, wherein the compound of formula (I) is bound to an inorganic base containing sodium, potassium, magnesium or calcium; or an organic base containing lysine, ethanolamine or N,N'-dibenzylethylenediamine.

The compounds of formula (I) may be chemically synthesized according to the process described by Tetsuhiro Nemoto et al.(*Tetrahedron Letters*, *41*, 9569-9574 (2000)) or Lan Xie et al.(*J. Med. Chem.*, *42*, 2662-2672 (1999)). Particularly, the compounds of formulas (1-a), (1-b) and (1-d) may be isolated from *Angelica gigas* according to the process described by Chi H-Y et al.(*vide supra*).

The compound of formula (I) exerts a higher analgesic effect than acetaminophen or aspirin, even at a low dose.

In contrast with its potent efficacy, the compound of formula (I) shows little toxicity in tests using mice. Moreover, the fact that *Angelica gigas* containing the compound of formula (I) has long been used as an ingredient in various herb medicine concretions without adverse side effects attests to its nontoxicty.

Therefore, the compound of formula (I) may be administered to a mammal in combination with a pharmaceutically acceptable carrier for alleviating pain. Therefore, the present invention provides a method for alleviating pain in a mammal which comprises administering an effective amount of the compound of formula (I) to the mammal.

Further, the present invention provides a pharmaceutical composition which comprises the compound of formula (I) as an active ingredient and a pharmaceutically acceptable carrier.

The pharmaceutical formulation may be prepared in accordance with any of the conventional procedures. In preparing the formulation, the active ingredient is preferably admixed or diluted with a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material acting as a vehicle, excipient or medium for the active ingredient. Thus, the formulations may be in the form of a tablet, pill, powder, sachet, elixir, suspension, emulsion, solution, syrup, aerosol, soft and hard gelatin capsule, sterile injectable solution, sterile packaged powder and the like.

Examples of suitable carriers, excipients, and diluents are lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, alginates, gelatin,

calcium phosphate, calcium silicate, cellulose, methyl cellulose, microcrystalline cellulose, polyvinylpyrrolidone, water, methylhydroxybenzoates, propylhydroxybenzoates, talc, magnesium stearate and mineral oil. The formulations may additionally include fillers, anti-agglutinating agents, lubricating agents, wetting agents, flavoring agents, emulsifiers, preservatives and the like. The compositions of the invention may be formulated so as to provide quick, sustained or delayed release of the active ingredient after their administration to a mammal by employing any of the procedures well known in the art.

The pharmaceutical composition of the present invention can be administered via various routes including oral, transdermal, subcutaneous, intravenous and intramuscular introduction. In case of human, a typical daily dose of the compound of formula (I) may range from about 1 to 100 mg/kg body weight, preferably 1 to 5 mg/kg body weight, and can be administered in a single dose or in divided doses.

However, it should be understood that the amount of the active ingredient actually administered ought to be determined in light of various relevant factors including the condition to be treated, the chosen route of administration, the age, sex and body weight of the individual patient, and the severity of the patient's symptom; and, therefore, the above dose should not be intended to limit the scope of the invention in any way.

The following Examples are intended to further illustrate the present invention without limiting its scope.

<u>Preparation Example 1</u>: Isolation of 3-methyl-but-2-enoic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2*H*,8*H*-pyrano[3,2-*g*]chromen-3-yl ester(Compound I-b) from *Angelica gigas*

1 kg of chopped *Angelica gigas* rhizome was extracted twice with 2 ℓ portions of 80 % methanol aqueous at 40 ℃ for 2 hours, and the extract solutions were combined, and dried under a vacuum to obtain 290 g of an extract.

The extract was subjected to systematic solvent fractionation using ethyl acetate, n-butanol and water. The ethyl acetate fraction contained Compound I-b, Compound I-d(2-methyl-but-2-enoic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2*H*,8*H*-pyrano[3,2-*g*]chromen-3-yl ester) and coumarin derivatives.

In order to isolate Compounds I-b and I-d, the ethyl acetate fraction was

subjected to silica gel column chromatography(SiO_2: 800g, $CHCl_3$:methanol=10:1) to obtain 6 fractions, and the second fraction was further fractionated by silica gel column chromatography(n-hexane:ethyl acetate=3:1) to obtain a mixture of Compounds I-b and I-d, the identities of which were confirmed by analysis with ^{1}H-NMR(400 MHz, $CDCl_3$), ^{13}C-NMR(100 MHz, $CDCl_3$) and EI+/MS.

35 g of the title compound was isolated from this mixture by silica gel column chromatography(230-240 mesh, n-hexane:ethyl acetate=3:1).

Preparation Example 2: Preparation of 7-hydroxy-8,8-dimethyl-7,8-dihydro-6*H*-pyrano[3,2-*g*]chromen-2-one(Compound I-a)

10 g of the mixture of Compounds I-b and I-d obtained in Preparation Example 1 was dissolved in 50 mℓ of 1:1 mixture of methanol and chloroform, and 30 mℓ of 10 % potassium hydroxide was added thereto. The resulting solution was refluxed at 80 ℃ for 2 to 3 days. 100 mℓ of water was added to the reaction mixture, and extracted four times with 100 mℓ portions of ethyl acetate. The combined ethyl acetate layer which contained Compounds I-a and I-b was concentrated under a reduced pressure and the concentrate was subjected to silica gel column chromatography(SiO_2: 250 g, hexane:ethyl acetate=1:1). The eluent was examined by conducting thin layer chromatography(hexane:ethyl acetate=1:1) employing UV lamp and fractions containing Compound I-a, which absorbs blue fluorescence at wavelengths of 254 and 365 nm, were collected. Compounds I-a and I-b have R_f values 0.2 and 0.7, respectively. The fractions thus collected were combined and concentrated under a reduced pressure. The concentrate was then subjected to silica gel column chromatography, three times in sequence using 3:1, 2:1 and 1:1 mixture of hexane and ethyl acetate in that order, to obtain 3.7 g of pure Compound I-a.

HPLC analysis condition:
Column: Si-60(250x4) Lichrosorb
Solvent: Hexane:ethyl acetate
UV detector: 340 nm
Flow rate: 1 mℓ/ min.
Retention time: 31 min.

Compound I-a:

^{1}H-NMR(400 MHz, $CDCl_3$): δ 1.37 (3H, s), 1.39 (3H, s), 2.83 (1H, dd, J=4.9, 16.6Hz), 3.10(1H, dd, J=5.9, 16.6Hz), 3.87 (1H, dd, 4.9, 5.9 Hz), 6.22 (1H, d, J=9.5 Hz), 6.78 (1H,s), 7.18 (1H,s), 7.57 (1H, d, J=9.5 Hz)

molecular weight: 246.2653

specific rotation [α]17D = + 173.1 ($CHCl_3$)

property : light-yellow prisms

melting point: 178 [methanol]

Preparation Example 3: Preparation of 6,7-dihydroxy-8,8-dimethyl-7,8-dihydro-6*H*-pyrano[3,2-*g*]chromen-2-one (Compound I-c)

To 5 mℓ of a mixture of t-butanol and water(1:1), 150 mg(0.75 mmol) of $K_3Fe(CN)_6$, 105 mg(0.75 mmol) of K_2CO_3, 4.4 mg(0.005 mmol) of 2,5-diphenyl-4,6-bis(9-O-dihydroquinyl)-pyrimidine and 1.8 mg(0.005 mmol) of $K_2OsO_2(OH)_4$ were added sequentially and dissolved at room temperature. The resulting solution was cooled to 0 ℃ and 23.7 mg(0.25 mmol) of methansulfonamide was added thereto. After the color of the resulting solution changed from yellow to orange, 57 mg(0.25 mmol) of chromen compound(benzopyrone)(Agarwal S. K. et al., *J Ethnopharmacol.*, *71*, 231-4 (2000)) was slowly added thereto. The resulting solution was stirred at 0 ℃ for two days. After completion of the reaction, an excess amount of $Na_2S_2O_5$, 10 mℓ of water and 10 mℓ of $CHCl_3$ were added thereto and the resulting solution was stirred for 30 min. The $CHCl_3$ layer was separated from the reaction mixture, dried over magnesium sulfate and the solvent was removed under a reduced pressure. The crude product thus obtained was subjected to column chromatography to obtained 49.8 mg(76%) of the title compound in a pure form.

Example 1: Acetic acid-induced Writhing Test Using Compound I-a

Compound I-a obtained in Preparation Example 2 was orally administered to 4-week-old ICR mice each weighing about 25 g at doses of 10, 25, 50 and 100 mg/kg, respectively. 0.25 mℓ of 0.7 % acetic acid was administered to the abdominal cavity of each of the mice and the writhing response was examined for 30 min. A group of mice not administered with

Compound I-a were used as a control.

Fig. 1, which shows numbers of writhing at various doses of Compound I-a, suggests that Compound I-a inhibits the writhing response induced by acetic acid in a dose-dependent manner.

Example 2: Formalin-induced Pain Test Using Compound I-a

Compound I-a obtained in Preparation Example 2 was orally administered to 4-week-old ICR mice each weighing about 25 g at doses of 10, 25, 50 and 100 mg/kg, respectively. After 30 min., 1 % formalin solution was administered to the rear feet of each of the mice, the pain-response behavior of each mouse, licking the foot or shivering, was observed during the initial 5 min.(phase 1) and during 20 min. to 40 min.(phase 2). As a control, the procedure was repeated with a group of mice not administered with Compound I-a.

Figs. 2A and 2B, which show the duration of the pain response(sec) of mice administered with various doses of Compound I-a at phases 1 and 2, respectively, suggest that Compound I-a reduces the pain response at phases 1 and 2 in a dose-dependent manner.

Example 3: Substance P-induced Pain Test Using Compound I-a

Compound I-a obtained in Preparation Example 2 was orally administered to 4-week-old ICR mice each weighing about 25 g at doses of 10, 25, 50 and 100 mg/kg, respectively. After 30 min., 0.7 μg of Substance P was intrathecally administered to each of the mice and for the next 30 min. the pain response behavior of each mouse, licking the foot or shivering, was measured. As a control, the procedure was repeated with a group of mice not administered with Compound I-a.

Fig. 3, which shows the duration of the pain response(sec) of mice administered with various doses of Compound I-a, suggests that Compound I-a reduces the pain response induced by Substance P in a dose-dependent manner.

Example 4: Glutamate-induced Pain Test Using Compound I-a

Compound I-a obtained in Preparation Example 2 was orally administered to 4-week-old ICR mice each weighing about 25 g at doses of 10,

25 and 50 mg/kg, respectively. After 30 min., 20 μg of glutamate was intrathecally administered to each of the mice and for the next 30 min. the pain response behavior was measured. As a control, the procedure was repeated with a group of mice not administered with Compound I-a.

Fig. 4, which shows the duration of the pain response(sec) of mice administered with various doses of Compound I-a, suggests that Compound I-a reduces the pain response induced by glutamate in a dose-dependent manner.

Example 5: Tail-flick Test Using Compound I-a

Compound I-a obtained in Preparation Example 2 was orally administered to 4-week-old ICR mice each weighing about 25 g at doses of 10, 25, 50 and 100 mg/kg, respectively. The tails of the mice were radiated with radient heat to stimulate thermal nociceptor and the time period during which each mouse flicks the tail due to the pain triggered by the radiation stimulus was measured to determine analgesia rate(%). As a control, the procedure was repeated with a group of mice not administered with Compound I-a.

Fig. 5A shows variations of analgesia rate(%) of the mice administered with Compound I-a in a dose of 100 mg/kg with time after radiation; and Fig. 5B shows analgesia rate(%) of the mice administered with various doses of Compound I-a. As can be seen from Figs. 5A and 5B, Compound I-a exhibits the highest analgesia rate at 30 min. after radiation and reduces the tail-flick response in a dose-dependent manner.

Example 6: Acetic acid-induced Writhing Test Using Compound I-b

Using Compound I-b obtained in Preparation Example 1 at doses of 50 and 100 mg/kg, respectively, the procedure of Example 1 was repeated.

Fig. 6, which shows numbers of writhing at various doses of Compound I-b, suggests that Compound I-b inhibits the writhing response at a dose of 100 mg/kg.

Example 7: Formalin-induced Pain Test Using Compound I-b

Using Compound I-b obtained in Preparation Example 1 at doses of 50 and 100 mg/kg, respectively, the procedure of Example 2 was repeated.

Figs. 7A and 7B, which show the duration of the pain response(sec) of

mice administered with various doses of Compound I-b at phases 1 and 2, respectively, suggest that Compound I-b reduces the pain response induced by formalin at phase 2 at a dose of 100 mg/kg.

Example 8: Substance P-induced Pain Test Using Compound I-b

Using Compound I-b obtained in Preparation Example 1 at doses of 50 and 100 mg/kg, respectively, the procedure of Example 3 was repeated.

Fig. 8, which shows the duration of the pain response(sec) of mice administered with various doses of Compound I-b, suggests that Compound I-b reduces the pain response induced by Substance P at a dose of 100 mg/kg.

Example 9: Glutamate-induced Pain Test Using Compound I-b

Using Compound I-b obtained in Preparation Example 1 at doses of 50 and 100 mg/kg, respectively, the procedure of Example 4 was repeated.

Fig. 9, which shows the duration of the pain response(sec) of mice administered with various doses of Compound I-b, suggests that Compound I-b reduces the pain response induced by glutamate at a dose of 100 mg/kg.

Example 10: Tail-flick Test Using Compound I-b

Using Compound I-b obtained in Preparation Example 1 at doses of 50 and 100 mg/kg, respectively, the procedure of Example 5 was repeated.

Fig. 10A shows variations of analgesia rate(%) of the mice administered with Compound I-b in a dose of 100 mg/kg with time after radiation; and Fig. 10B shows analgesia rate(%) of the mice administered with various doses of Compound I-b. As can be seen from Figs. 10A and 10B, Compound I-a exhibits the highest analgesia rate at 30 min. after radiation and inhibits the tail-flick response in a dose-dependent manner.

Example 11: Acetic acid-induced Writhing Test Using Compound I-c

Using Compound I-c obtained in Preparation Example 3 at doses of 10, 25, 50 and 100 mg/kg, respectively, the procedure of Example 1 was repeated.

Fig. 11, which shows numbers of writhing at various doses of Compound I-c, suggests that Compound I-c inhibits the writhing response

induced by acetic acid at doses of 50 and 100 mg/kg.

Example 12: Formalin-induced Pain Test Using Compound I-c

Using Compound I-c obtained in Preparation Example 3 at doses of 10, 25 and 50 mg/kg, respectively, the procedure of Example 2 was repeated.

Figs. 12A and 12B, which show the duration of the pain response(sec) of mice administered with various doses of Compound I-c at phases 1 and 2, respectively, suggest that Compound I-c reduces the pain response induced by formalin at phase 2 at a dose of 100 mg/kg.

Example 13: Glutamate-induced Pain Test Using Compound I-c

Using Compound I-c obtained in Preparation Example 3 at doses of 10, 25 and 50 mg/kg, respectively, the procedure of Example 4 was repeated.

Fig. 13, which shows the duration of the pain response(sec) of mice administered with various doses of Compound I-c, suggests that Compound I-c reduces the pain response induced by glutamate at doses of 25 and 50 mg/kg.

Comparative Example 1: Acetic acid-induced Writhing Test Using Acetaminophen

Using acetaminophen at doses of 300 and 600 mg/kg, respectively, the procedure of Example 1 was repeated.

Fig. 14, which shows numbers of writhing at various doses of acetaminophen, suggests that acetaminophen inhibits the writhing response induced by acetic acid at high doses of 300 and 600 mg/kg.

Comparative Example 2: Formalin-induced Pain Test Using Acetaminophen

Using acetaminophen at doses of 300 and 600 mg/kg, respectively, the procedure of Example 2 was repeated.

Figs. 15A and 15B, which show the duration of the pain response(sec) of mice administered with various doses of acetaminophen at phases 1 and 2, respectively, suggest that acetaminophen reduces the pain response induced by formalin at phases 1 and 2 at high doses of 300 and 600 mg/kg.

Comparative Example 3: Substance P-induced Pain Test Using Acetaminophen

Using acetaminophen at doses of 100 and 300 mg/kg, respectively, the procedure of Example 3 was repeated.

Fig. 16, which shows the duration of the pain response(sec) of mice administered with various doses of acetaminophen, suggests that acetaminophen reduces the pain response induced by Substance P at high doses of 100 and 300 mg/kg.

Comparative Example 4: Glutamate-induced Pain Test Using Acetaminophen

Using acetaminophen at doses of 100 and 300 mg/kg, respectively, the procedure of Example 4 was repeated.

Fig. 17, which shows the duration of the pain response(sec) of mice administered with various doses of acetaminophen, suggests that acetaminophen reduces the pain response induced by glutamate at high doses of 100 and 300 mg/kg.

Comparative Example 5: Tail-flick Test Using Acetaminophen

Using acetaminophen at doses of 300 and 600 mg/kg, respectively, the procedure of Example 5 was repeated.

Fig. 18A and 18B show variations of analgesia rate(%) of the mice administered with acetaminophen at doses of 300 and 600 mg/kg, respectively, with time after radiation. As can be seen from Figs. 18A and 18B, acetaminophen at doses of 300 and 600 mg/kg exhibits the highest analgesia rate at 30 min. after radiation.

Comparative Example 6: Acetic acid-induced Writhing Test Using Aspirin

Using aspirin at doses of 10, 25, 50, 100, 200 and 300 mg/kg, respectively, the procedure of Example 1 was repeated.

Fig. 19, which shows numbers of writhing at various doses of aspirin, suggests that aspirin almost dose not inhibit the writhing response induced by acetic acid.

Comparative Example 7: Formalin-induced Pain Test Using Aspirin

Using aspirin at doses of 10, 25, 50, 100, 200 and 300 mg/kg, respectively, the procedure of Example 2 was repeated.

Figs. 20A and 20B, which show the duration of the pain response(sec) of mice administered with various doses of aspirin at phases 1 and 2, respectively, suggest that aspirin does not reduce the pain response induced by formalin at phase 1 and reduces it at phase 2 only at a high dose of 100 mg/kg or more.

Comparative Example 8: Substance P-induced Pain Test Using Aspirin

Using aspirin at doses of 120 and 240 mg/kg, respectively, the procedure of Example 3 was repeated.

Fig. 21, which shows the duration of the pain response(sec) of mice administered with various doses of aspirin, suggests that aspirin reduces the pain response induced by Substance P at a high dose of 240 mg/kg.

Comparative Example 9: Glutamate-induced Pain Test Using Aspirin

Using aspirin at doses of 120 and 240 mg/kg, respectively, the procedure of Example 4 was repeated.

Fig. 22, which shows the duration of the pain response(sec) of mice administered with various doses of aspirin, suggests that aspirin reduces the pain response induced by glutamate at high doses of 120 and 240 mg/kg.

Comparative Example 10: Tail-flick Test Using Aspirin

Using aspirin at doses of 100 mg/kg, the procedure of Example 5 was repeated.

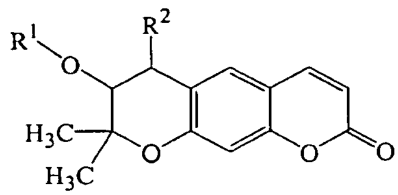
Fig. 23, which shows variations of analgesia rate(%) of the mice administered with aspirin at a dose of 100 mg/kg with time after radiation. As can be seen from Fig. 23, aspirin at a dose of 100 mg/kg exhibits the highest analgesia rate at 30 min. after radiation but its value is tiny.

While the subject invention has been described and illustrated with reference to the preferred embodiments only, it may be apparent to those skilled

in the art that various changes and modifications can be made therein without departing from the spirit and scope of the present invention which is defined in the appended claims.

What is claimed is :

1. A use of decursinol or a derivative thereof represented by formula (I) for alleviating pain in a mammal:



(I)

wherein R^1 is hydrogen, 3-methyl-but-2-enoyl or 2-methyl-but-2-enoyl; and R^2 is hydrogen or hydroxy.

2. The use of claim 1, wherein the compound is selected from the group consisting of:

7-hydroxy-8,8-dimethyl-7,8-dihydro-6*H*-pyrano[3,2-*g*]chromen-2-one;

3-methyl-but-2-enoic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2*H*,8*H*-pyrano[3,2-*g*]chromen-3-yl ester;

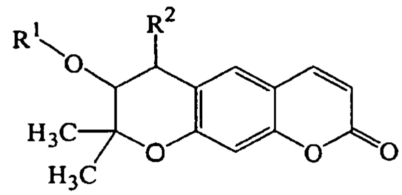
6,7-dihydroxy-8,8-dimethyl-7,8-dihydro-6*H*-pyrano[3,2-*g*]chromen-2-one; and

2-methyl-but-2-enoic acid 2,2-dimethyl-8-oxo-3,4-dihydro-2*H*,8*H*-pyrano[3,2-*g*]chromen-3-yl ester.

3. The use of claim 1, wherein the compound is administered to the mammal in the form of a pharmaceutical composition containing same.

4. The use of claim 3, wherein the effective amount of the compound contained in the pharmaceutical composition ranges from 1 to 100 mg/kg body weight/day.

5. A method for alleviating pain in a mammal, which comprises administering an effective amount of a compound of formula (I) to the mammal:



(I)

wherein R^1 is hydrogen, 3-methyl-but-2-enoyl or 2-methyl-but-2-enoyl; and R^2 is hydrogen or hydroxy.

Fig. 1

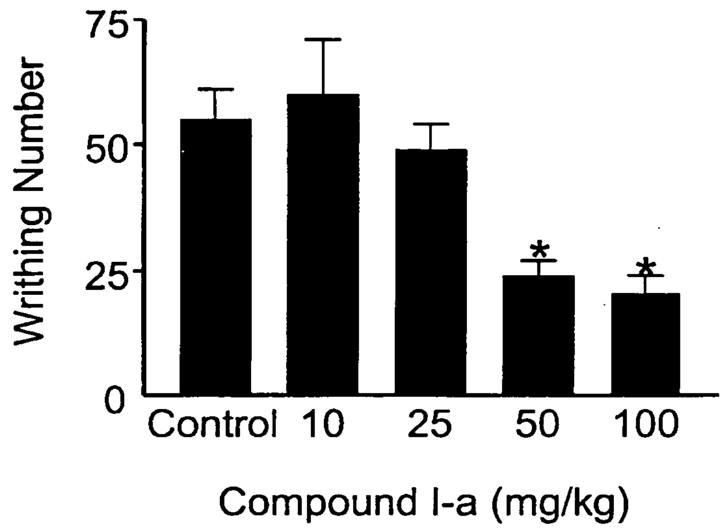

Writhing Number
75
50
25
0
Control 10 25 50 100
Compound I-a (mg/kg)

Fig. 2A

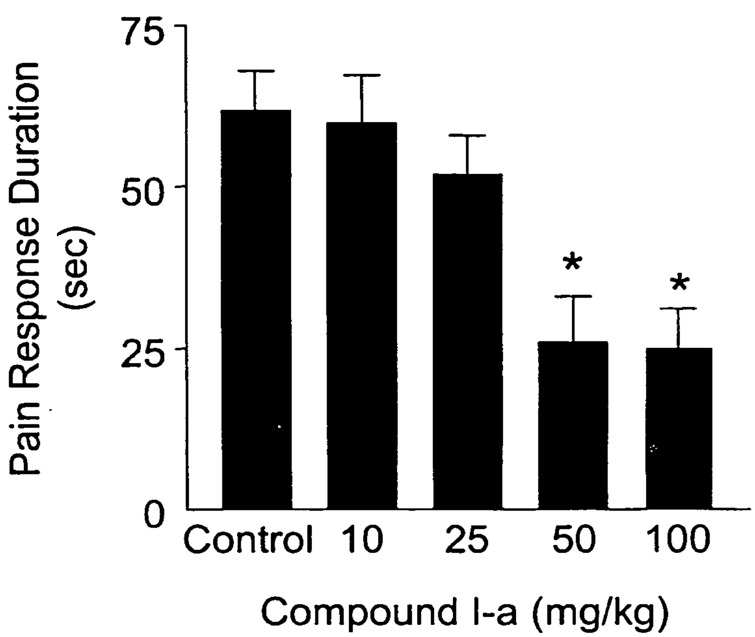

Pain Response Duration (sec)
75
50
25
0
Control 10 25 50 100
Compound I-a (mg/kg)

Fig. 2B

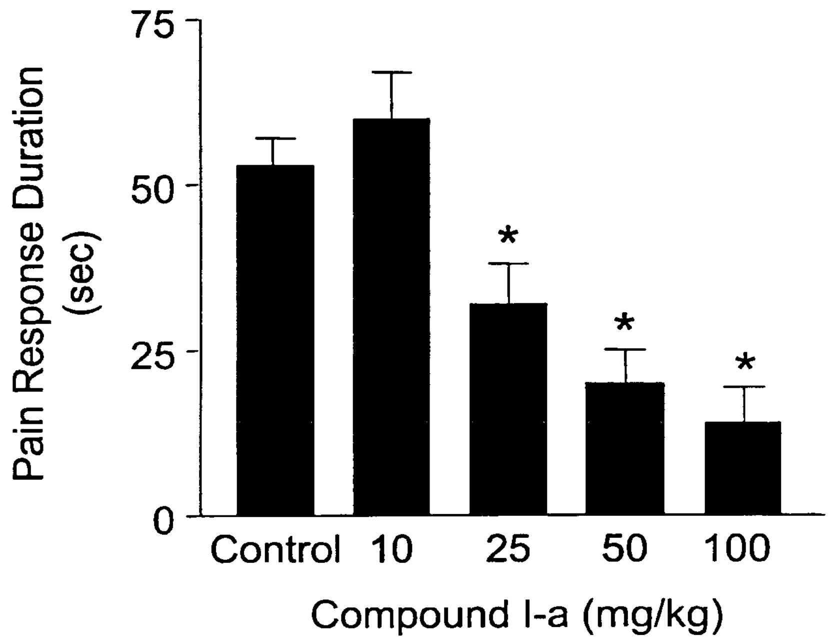

75
50
25
0
Pain Response Duration (sec)
*
*
*
Control
10
25
50
100
Compound I-a (mg/kg)

Fig. 3

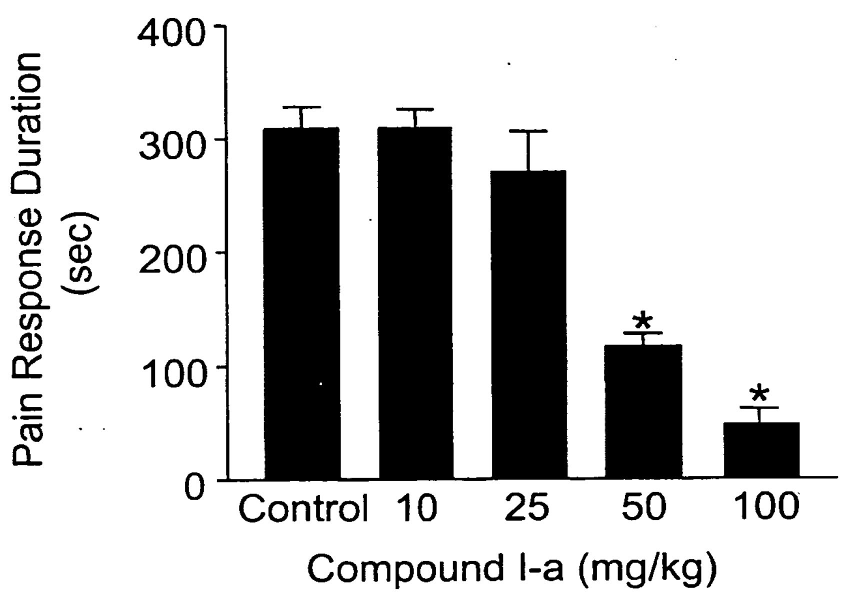

400
300
200
100
0
Pain Response Duration (sec)
*
*
Control
10
25
50
100
Compound I-a (mg/kg)

Fig. 4

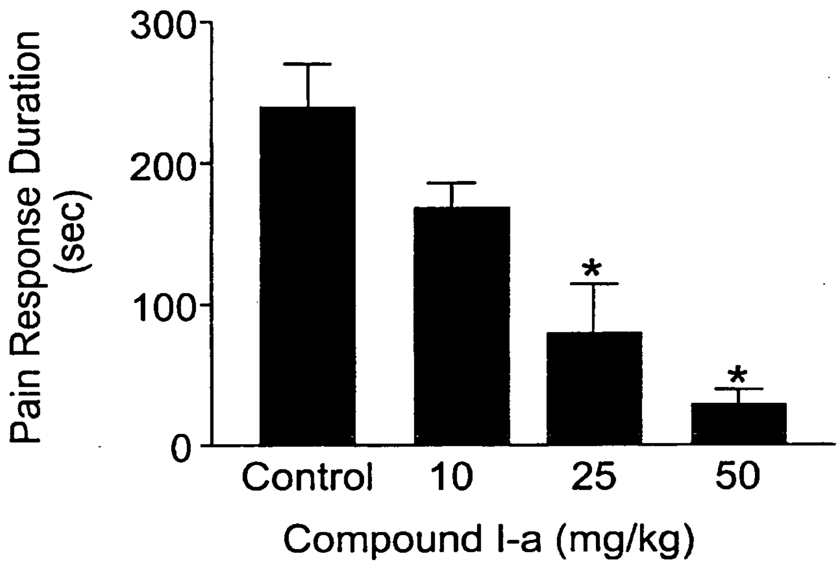

Pain Response Duration (sec)
300
200
100
0
*
*
Control
10
25
50
Compound I-a (mg/kg)

Fig. 5A

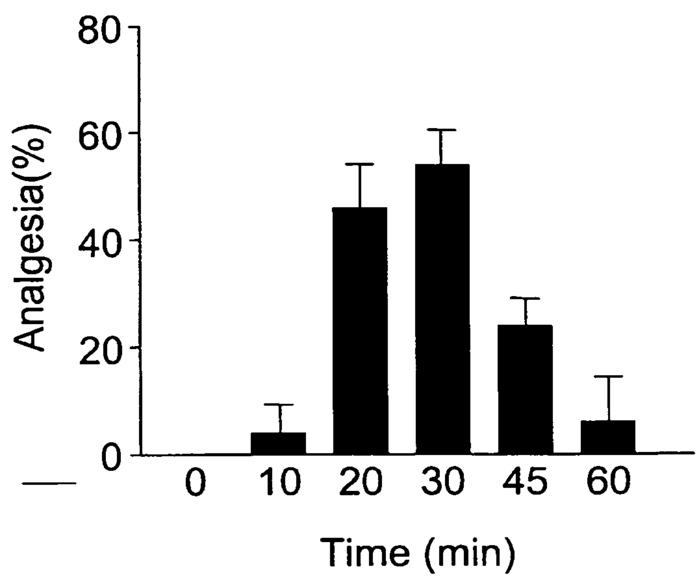

Analgesia(%)
80
60
40
20
0
0
10
20
30
45
60
Time (min)

Fig. 5B

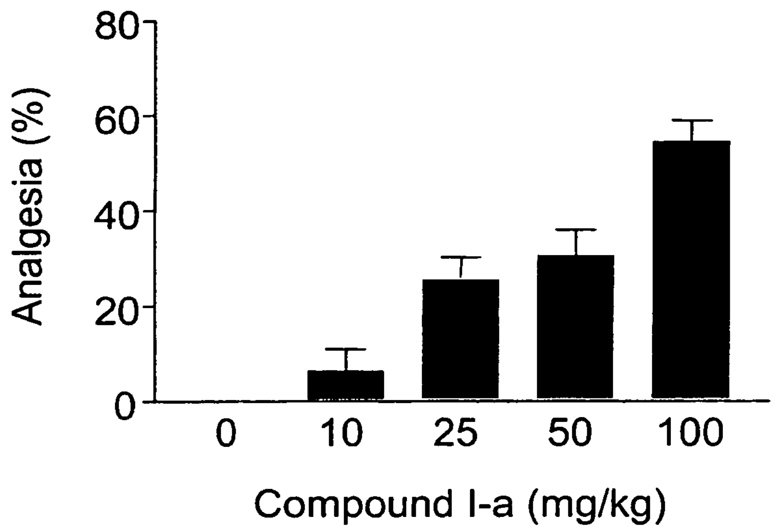

80
60
40
20
0
Analgesia (%)
0
10
25
50
100
Compound I-a (mg/kg)

Fig. 6

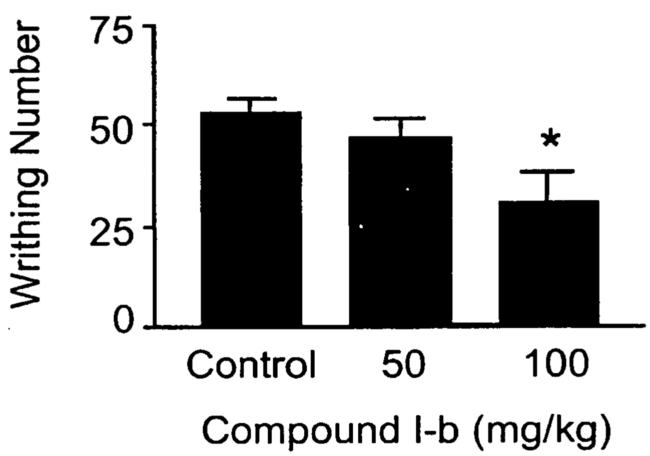

75
50
25
0
Writhing Number
*
Control
50
100
Compound I-b (mg/kg)

Fig. 7A

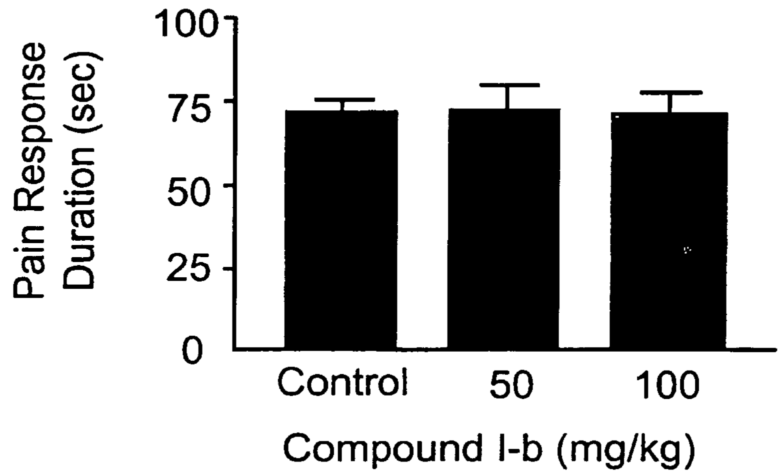

Pain Response Duration (sec)
100
75
50
25
0
Control
50
100
Compound I-b (mg/kg)

Fig. 7B

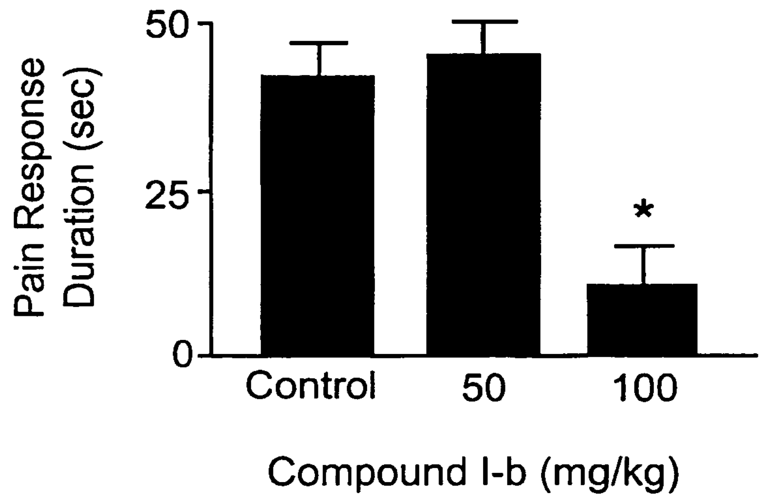

Pain Response Duration (sec)
50
25
0
*
Control
50
100
Compound I-b (mg/kg)

Fig. 8

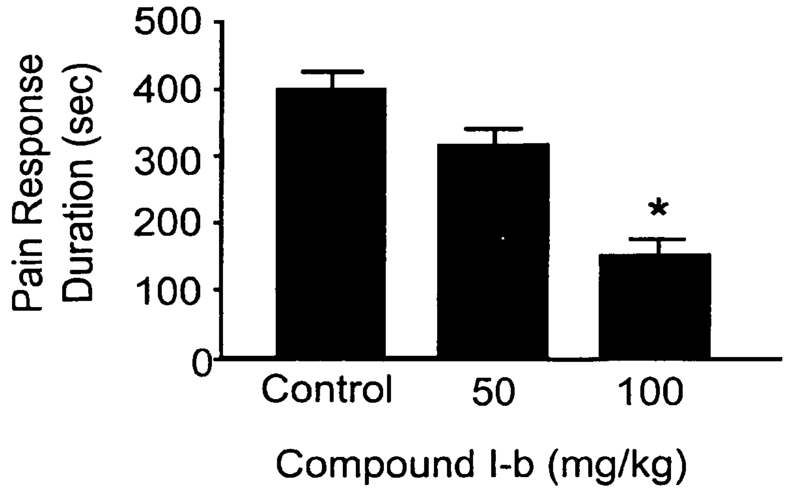

500
400
300
200
100
0
Pain Response Duration (sec)
*
Control
50
100
Compound I-b (mg/kg)

Fig. 9

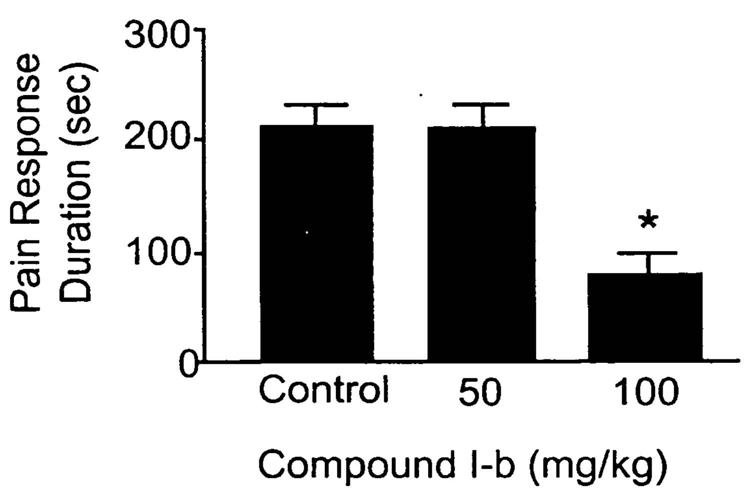

300
200
100
0
Pain Response Duration (sec)
*
Control
50
100
Compound I-b (mg/kg)

Fig. 10A

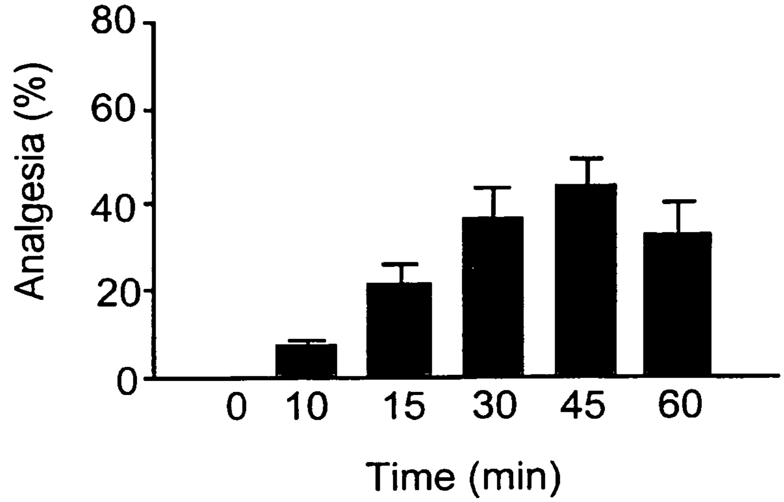


Fig. 10B

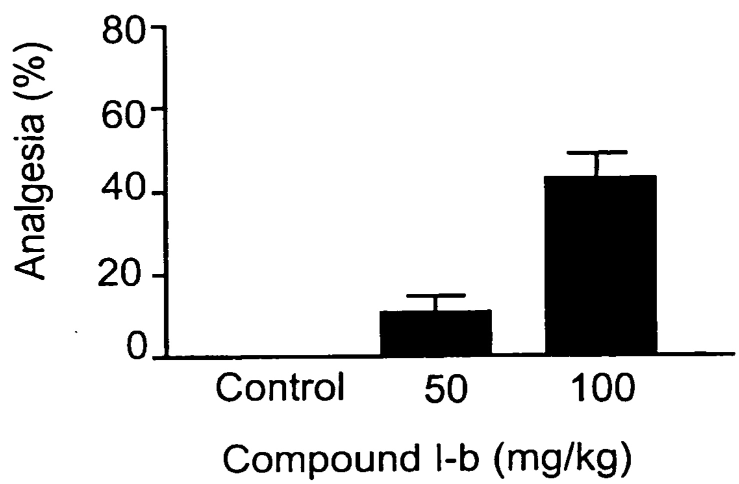


Fig. 11

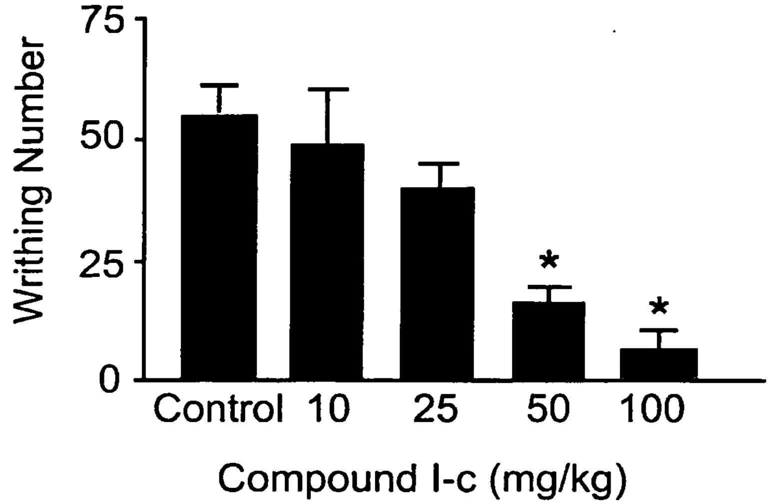


Fig. 12A

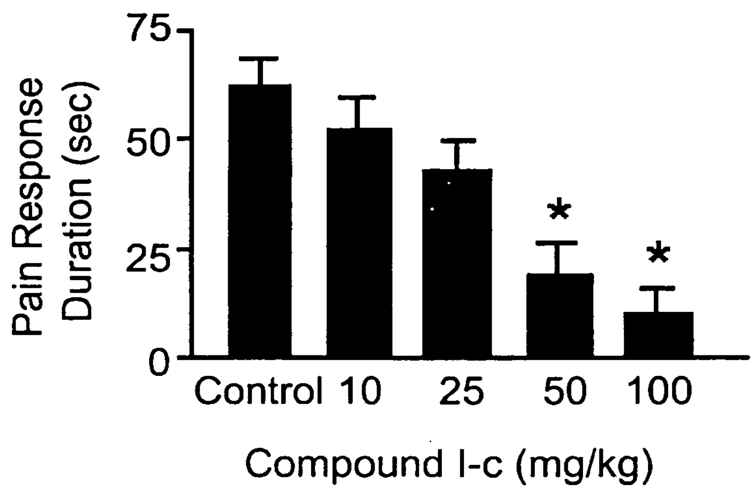


Fig. 12B

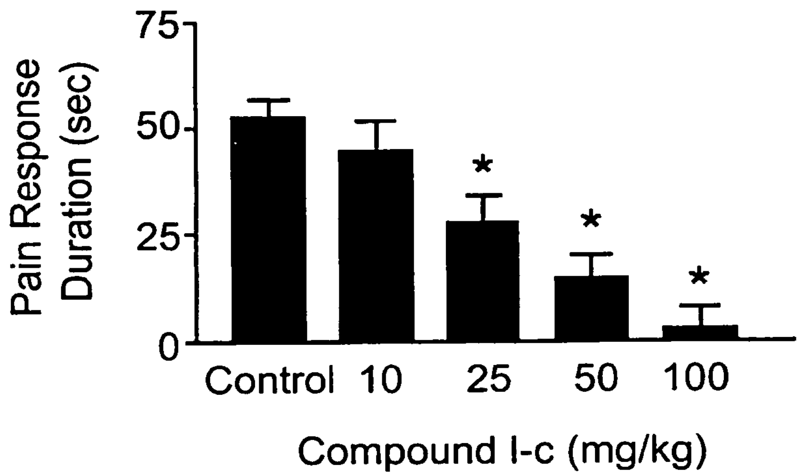


Fig. 13

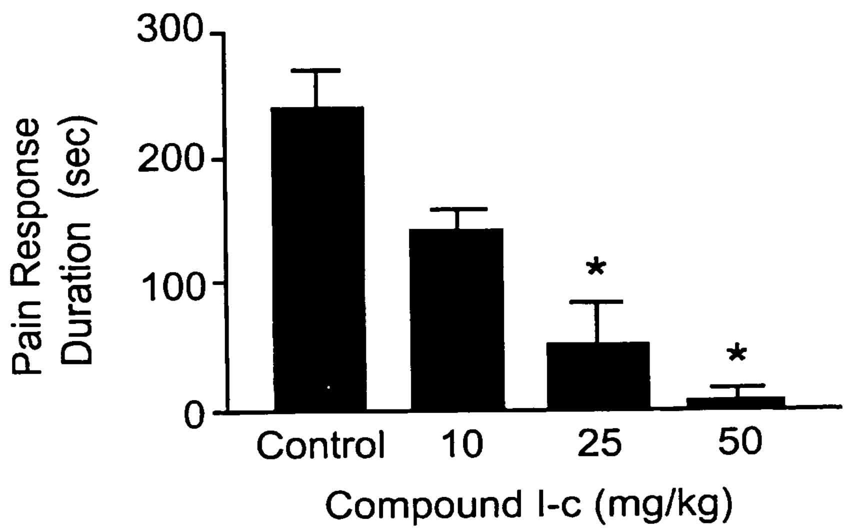


Fig. 14

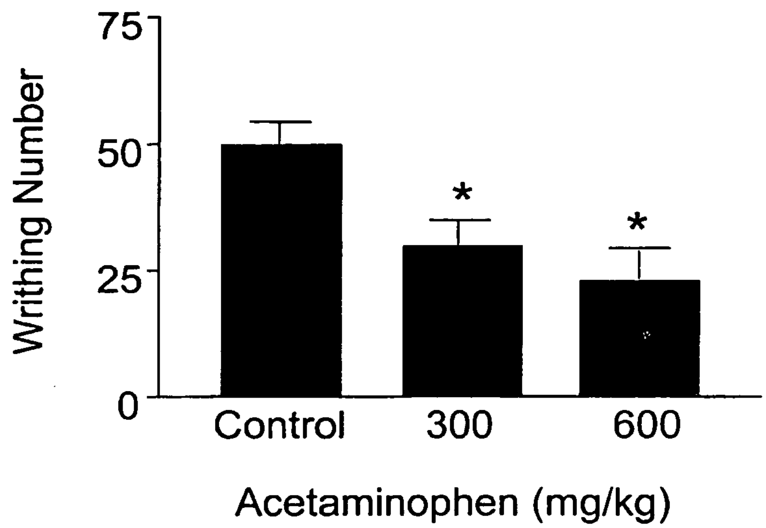


Fig. 15A

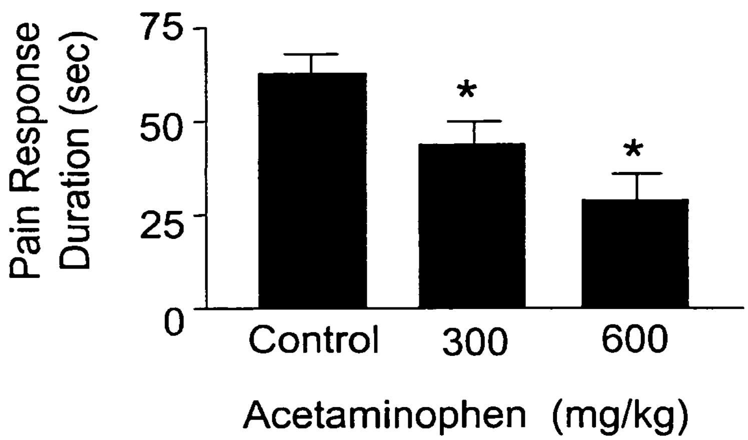


Fig. 15B

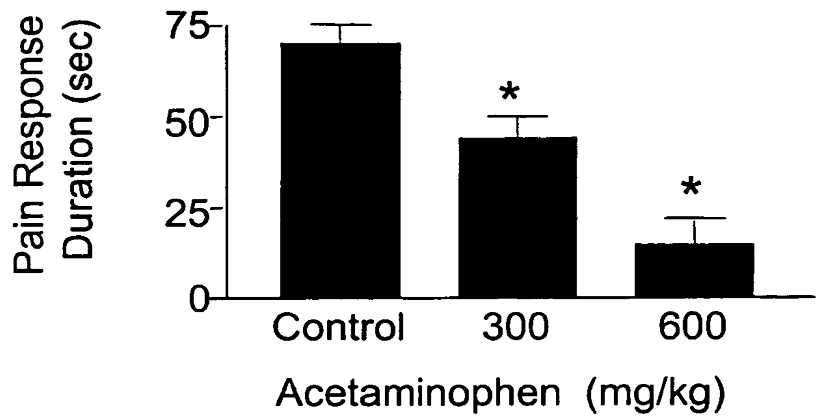


Fig. 16

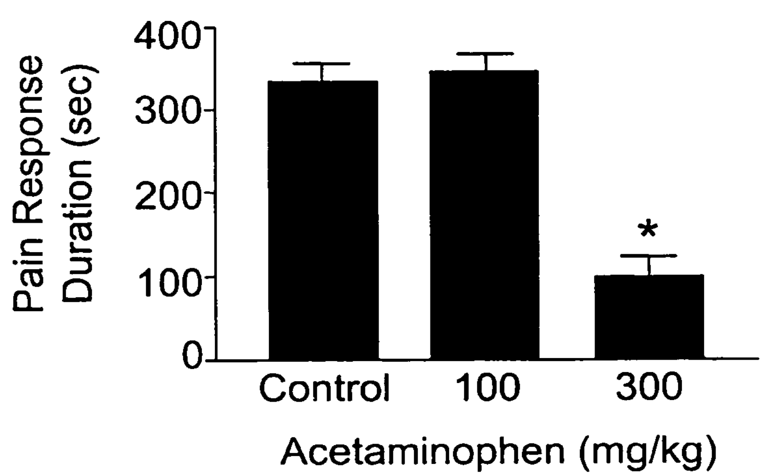


Fig. 17

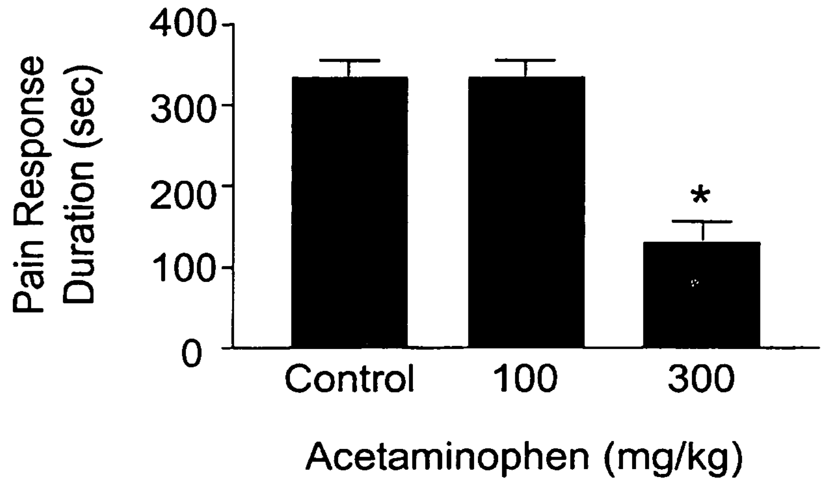


Fig. 18A

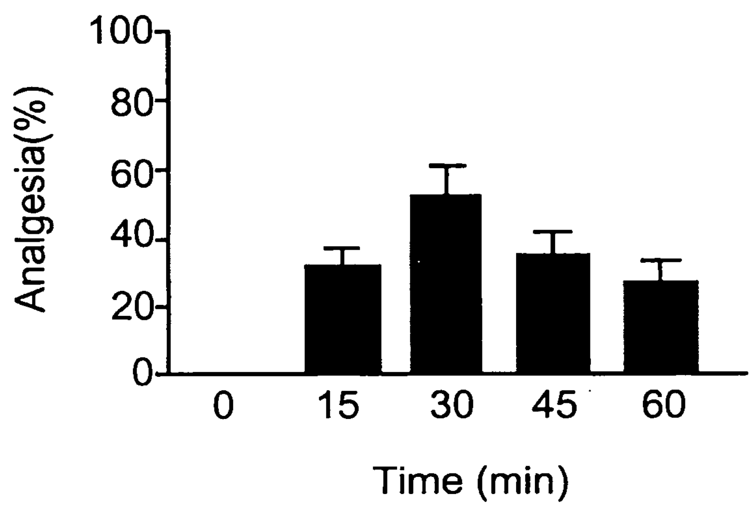


Fig. 18B

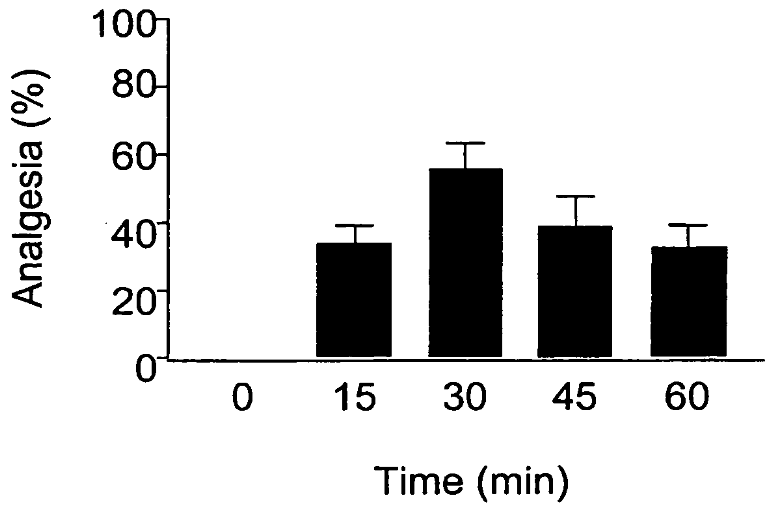


Fig. 19

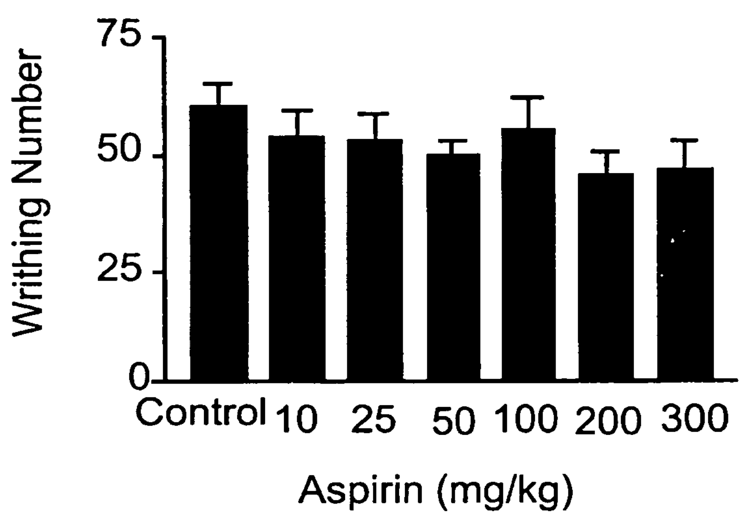


Fig. 20A

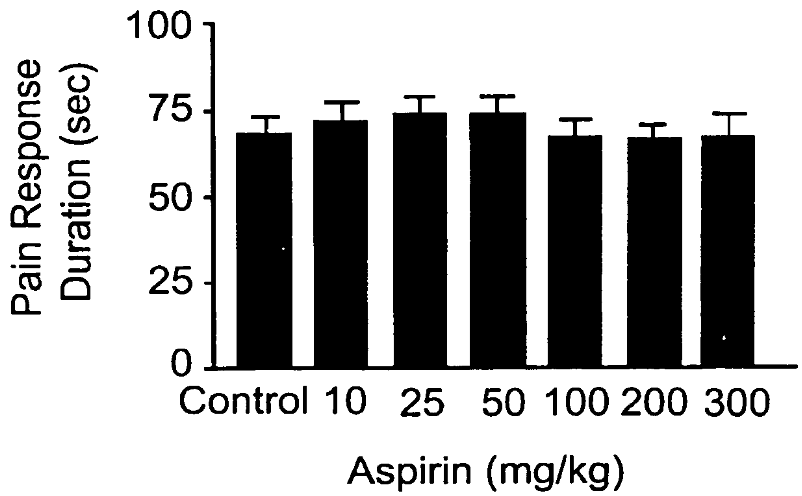


Fig. 20B

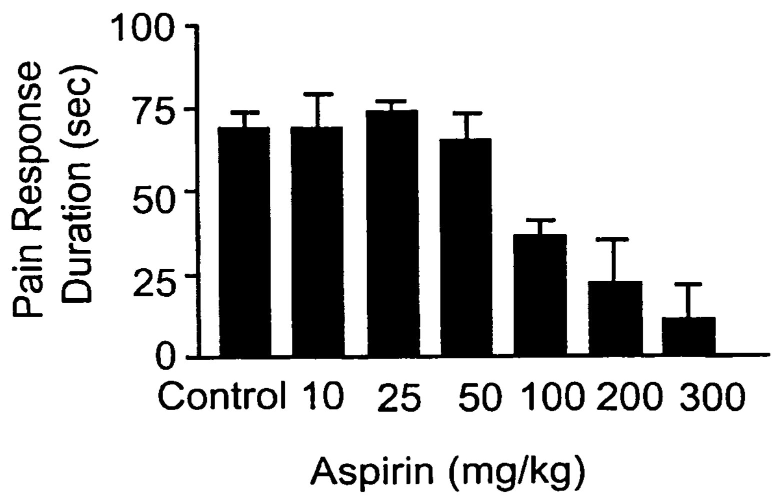


Fig. 21

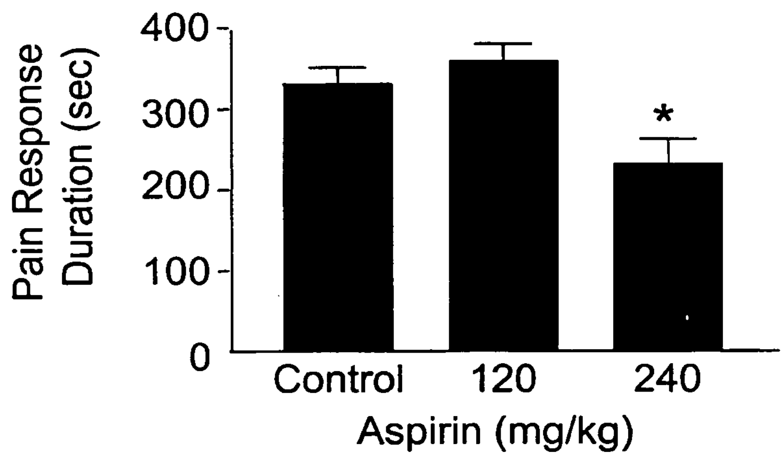

Pain Response Duration (sec)
400
300
200
100
0
*
Control
120
240
Aspirin (mg/kg)

Fig. 22

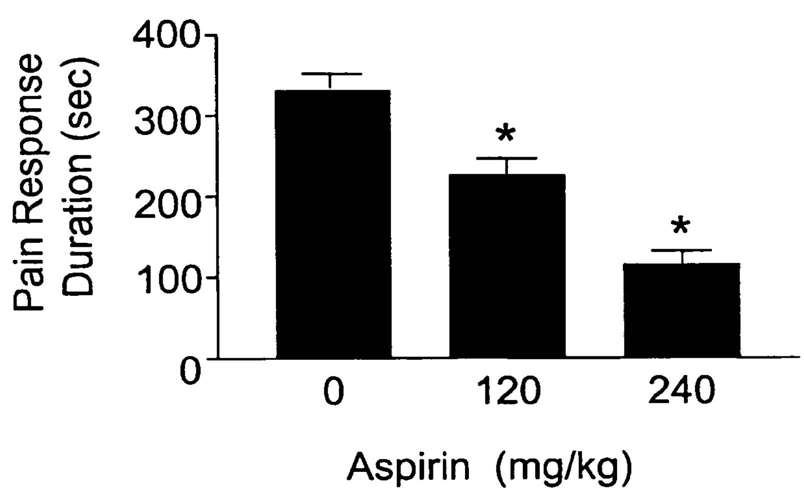

Pain Response Duration (sec)
400
300
200
100
0
*
*
0
120
240
Aspirin (mg/kg)

Fig. 23